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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/816,790 | 03/22/2001 | Keith D. Allen | R-855 | 5557 |

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EXAMINER

QIAN, CELINE X

| ART UNIT | PAPER NUMBER |
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1636

10

DATE MAILED: 03/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/816,790

Applicant(s)

ALLEN ET AL.

Examiner

Celine Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 11-16 and 22-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 17-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Claims 1-25 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the inventions in Groups I-VI are related and thus a search can be made without serious burden on the Examiner. Specifically, Applicants argue that the methods of Groups II and III, II and V, III and V share a common starting material, the transgenic knockout mouse, therefore, the inventions are related. Applicants further argue that the method of Group III can produce the composition of Group VI. This is not found persuasive because of the following reasons. The Examiner agree with Applicants' arguments with regard to Groups II and III, II and V, III and V that they share a common starting material, however, the transgenic knockout mouse is not the only starting material in these methods. The agents being tested are also part of starting material and they are different for each group. For instance, an agent that modulates the expression of a gene is different from an agent that modulates the function of said gene. With regard to Group III and VI, an agent that modulates the function of a gene is not necessary able to ameliorate a symptom caused by the disruption of said gene. Moreover, even the agents are same or similar, the steps that determine whether the gene function is modulated and the symptom is ameliorated are different. Therefore, the inventions of Groups I-VI are patentably distinct for the same reasons set forth in the prior office action mailed on 12/3/01. The Examiner agrees that the inventions are related, however, the inventions are patentably distinct, and the search is not co-extensive. Therefore, a search of all the groups will be a serious burden.

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The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-16 and 22-25 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1-10 and 17-21 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a sulfotransferase gene knockout mouse exhibiting hyperactive and aggressive behavior, does not reasonably provide enablement for any other sulfotransferase gene knockout non-human animals without said phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention is a sulfotransferase gene knockout non human animal. The specification discloses the generation of a mouse having sulfotransferase gene disrupted by homologous recombination in mouse ES cells and said mouse exhibit hyperactive and aggressive behavior (see page 60).

Since homologous recombination is required for gene targeting method as employed by the specification, embryonic stem cell technology must be available to carry out the method. At the time of the invention, no embryonic stem cell other than mouse was isolated as indicated by the art (Osterrieder & Wolf, Rev. sci. tech. Off. int. Epiz., vol. 17, no.1, 351-364, 1998). The

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guidance of specification is limited and does not provide a method as to obtain ES cells from other animals. The specification only teaches generation of a sulfotransferase gene knockout mouse by using ES cells containing disrupted sulfotransferase gene achieved by homologous recombination. The specification does not teach the generation of ES cells of other non-human animals. Further the specification does not teach the generation of a sulfotransferase gene knockout non human animal by other methods. Lack of guidance from specification, one skilled in the art would turn to prior art for guidance to make a sulfotransferase gene knockout non-human animal other than mouse. However, the prior art does not teach gene targeting methods other than homologous recombination. The art does not teach how to generate embryonic stem cells from non human animals other than mouse. Therefore, one skilled in the art would have to engage in undue amount of experimentation to make the claimed invention, a sulfotransferase gene knockout non-human animal.

Claims 8 do not recite any particular phenotype for a transgenic non-human animal comprising a disruption in a sulfotransferase gene. However, the phenotype exhibited by the sulfotransferase gene knockout non-human animal as a consequence of gene knockout, as disclosed in the specification, is required to enable the use of the non-human animal to identify agents that ameliorates aggressive behavior, for example. The specification does not teach how to use the non-human animals lacking this phenotype. Therefore, one skilled in the art would have to engage in undue amount of experimentation to use the claimed invention.

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous sulfotransferase knockout mouse lacks production of

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functional sulfotransferase protein, does not reasonably provide enablement for a heterozygous sulfotransferase knockout mouse or a sulfotransferase gene disrupted mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is a transgenic mouse comprising a disruption in a sulfotransferase gene and exhibits phenotype comprising aggressive, hyperactive, increased activity and decreased anxiety behavior; and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using a sulfotransferase construct (see page 55-60, examples 1-4). The specification further discloses that the homozygous knockout mice exhibit the phenotype comprising hyperactive and aggressive behavior (see page 60, lines 12-27).

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, col.1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous sulfotransferase knockout mouse. Claims 17, 18, 20 and 21 encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a sulfotransferase knockout mouse is unpredictable.

The specification discloses that the word "disruption" comprises alter or replace a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by

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inhibiting its production partially or completely or by enhancing the normal product's activity (see page 9, lines 19-26). However, it is not known in the prior art that such "disruption," would produce the phenotype as disclosed by the specification. The specification only discloses a mouse with two alleles of sulfotransferase disrupted by inserting a selection marker that exhibits the phenotype comprising aggressive, hyperactive behavior. Thus, the phenotype of a transgenic mouse comprising a "disruption," as defined by the specification, in a sulfotransferase is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic knockout animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10, 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. As such, the metes and bounds of the claim cannot be established.

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Regarding claims 9 and 21, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown.

Regarding claims 17-21, the "activity" renders the claims indefinite because it is unclear that the nature of the activity applicants is referring to. In other words, it is not clear how "increased activity" is different from "hyperactive."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Kong et al. (1993, Biochimica et Biophysica Acta, vol. 1171, 315-318).

The claims are drawn to a sulfotransferase gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a

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sulfotransferase gene, and a method of producing a transgenic mouse comprising a disruption in a sulfotransferase gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from *hprt* and *int-2* respectively, and a neo selection marker in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a sulfotransferase gene target construct and knockout mouse.

Kong et al. teach the cloning of a mouse sulfotransferase gene, *mST*, from mouse liver. They provide the cloned coding sequence for sulfotransferase gene (see page 316, figure 1). Kong et al. also teach that the sulfotransferase has been implicated in the activation of mutagens and carcinogens (see page 318, 1st col., 2nd paragraph, lines 1-6).

It would have been obvious to one in the ordinary art to make a sulfotransferase knockout mouse. The ordinary artisan would have been motivated to knockout the function of sulfotransferase gene in a mouse to study the role this gene plays in the activation of mutagens and carcinogens in mouse (see page 318, 1st col., 2nd paragraph, lines 1-6). The ordinary artisan would have had reasonable expectation of success because of the teachings of Mansour et al.,

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who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Kong et al., who teach the coding sequence of the mouse sulfotransferase gene, and also teach the importance of this gene in activation of mutagens and carcinogens. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
March 11, 2002


REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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